APPLN. FILING DATE: OCTOBER 9, 2001

TITLE: BILE-ACID CONJUGATES FOR PROVIDING SUSTAINED

SYSTEMIC CONCENTRATIONS OF DRUGS

INVENTOR(S): CUNDY, ET AL.

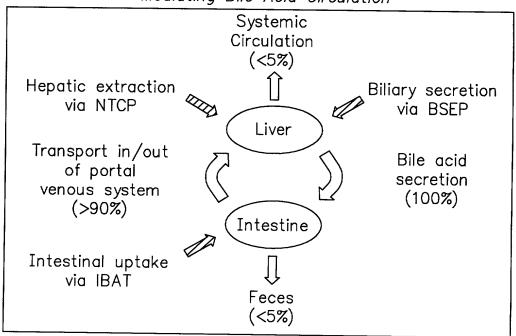
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FIG. 1

FIG. 2The Enterohepatic Circulation with Key Transporter Proteins
Mediating Bile Acid Circulation



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FIG. 3

Bile Acid Conjugates of HMG-CoA Reductase Inhibitor

FIG. 5

FmocNH
$$CO_2H$$
 2. H_2N 2. H_2N 3. DBU/DMF

1. CICO₂Et/NEt₃
2. H₂N CO₂H R H N CO₂H
3. DBU/DMF (2) H₂N (11)

"OH

3. NaOH/MeOH

(8)

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3/5 C02H NH₂ (7)1. CICO2Et/NEt3 $\widehat{\mathbf{E}}$ 3. NaOH/MeOH ΙŹ (e) エ 0: (d6)ভ F₀ ³ کOH R=H <u>©</u> $\overline{\epsilon}$ 工 Also synthesized from ursodeoxycholic acid: F/G. 4 I (96) 1. CICO₂Et/NEt₃ $\widehat{\mathbb{C}}$ ~i 0= (ae) 6) HO.,,, 9

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(10) 2. (11)

3. DBU/DMF

FIG. 7

$$H_2N$$
 H_2N
 H_2N
 H_3N
 H_4N
 H_5N
 H_5N

FIG. 8

1. CICO₂Et/NEt₃

2), H₂O

(22)
$$\frac{1. 2,4,6-Cl_3C_6H_2C(0)Cl}{Et_3N, DMAP}$$

(19)

2. TFA

3. Na⁺ exchange resin H₂O/MeOH

4. H₂, Pd/C, EtOH

EtOH
$$H_2N$$

$$(23)$$

$$H$$

$$CO_2Na$$

$$(23)$$

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